REMARKS

Discussion of Claim Amendments

Claims 21, 22, 38, 39, 44, 46, 48, and 56 have been amended to expedite the prosecution of this application. Claims 26, 30 and 35 have been amended to correct minor inconsistencies. The amended claims are separated by the original claims and specification, e.g., original claim 1 for the ratio of the active substance to the surface modifier and thermoprotecting agent, original claim 10 for the amount of the surface modifier, and page 8 lines 16-18 for the ratio of the drug to the phospholipid surface modifier. No new matter has been added.

The Office Action

The Office Action sets forth the following grounds for rejection: (1) claims 38-54 and 56-57 are rejected under 35 USC § 112, first paragraph, for an alleged non-enablement; and (2) claim 48 and 56 are rejected under 35 USC § 112, second paragraph, for an alleged indefiniteness; (3) claims 21-38, 40-54, and 56-57 are rejected under 35 USC § 112, second paragraph, for an alleged indefiniteness; (4) claims 21-54 and 56-57 are rejected under 35 USC § 103(a), as allegedly unpatentable over U.S. Patent No. 4,629,626 (Miyata et al.) in view of U.S. Patent No. 5,858,410 (Muller et al.); and (5) claims 38-54 and 56-57 are rejected under 35 USC § 112, first paragraph, for certain alleged non-enablement.

The Present Invention

The present invention is directed to an aqueous suspension comprising surface stabilized drug particles. Claims 21-46, 48-54, and 56-57 are currently pending. A set of pending claims is attached.

Discussion of Rejections

Claims 38 and 39 have been amended to exclude surfactants which coagulate on steam sterilization. Claims 40-46, 48-54 and 56-57 are dependent upon claim 38. In view of the foregoing, the section 112, first paragraph rejection alleging that claims 38-54 and 56-57 are not enabled for a suspension with surfactants should be withdrawn.

Applicants have amended claims 48 and 56. The amended claims meet the statutory requirement of section 112, second paragraph. In view of the foregoing, the indefiniteness rejection of claims 48 and 56 should be withdrawn.

Applicants have amended claims 21, 22, and 38 by deleting the term "substantially". Claims 23-37, 40-54 and 56-57 are dependent. In view of the foregoing, the indefiniteness rejection of claims 21-38, 40-54 and 56-57 should be withdrawn.

Applicants respectfully traverse the obviousness rejection of claims 21-54 and 56-57.

The Office Action cites Miyata et al. as teaching "autoclaving a suspension under nitrogen (Col. 9, lines 31-38) to maintain a composition stable to oxidation (Col. 9, line 64 through Col. 10, line 2)." The Office Action also states "It would have been obvious to one of ordinary skill to improve the stability of the Muller et al. suspension by autoclaving under nitrogen in view of Miyata et al."

However, one skilled in the art would not be led to use of nitrogen as disclosed in the autoclave process of Miyata et al. in order to improve the stability of the Muller et al. suspension. The process of Miyata et al. teaches away from the current invention.

Miyata et al. discloses that autoclaving under nitrogen causes a change to the composition undergoing a hydrothermal process to produce a new product that is more stable to oxidation than the starting composition. Such a change in chemical reactivity to oxidation can occur only if there is a change in some component of the chemical bonds of the product relative to the chemical bonds of the starting composition. This is contrary to the current invention. In the current invention, the suspension survives the autoclave process without a change in the composition of the drug.

Specifically, Miyata et al. discloses (at claim 1 and elsewhere) a hydrothermal process used to produce a product from a compound (I) having a hydrotalcite-like structure:

$$(Fe^{2+}, Mg^{2+})x(Al^{3+}, Fe^{3+})_2(OH)_{2x+6-n-z}(A^{n-})_z.mH_2O \qquad (I)$$

by treatment of the compound (I) between 100 and 200°C in an aqueous medium. In this process, compound (I) is changed into a different composition by the hydrothermal treatment. The composition so produced is more stable to subsequent air oxidization. Miyata et al. discloses (Col. 1, line 18) that the products produced after hydrothermal treatment "...have better oxidation resistance" (stability) to conventional products..." In contrast, the sterilization process of the present invention does not change a starting drug compound into a new drug product by application of thermal treatment in an aqueous environment under nitrogen.

The use of nitrogen in the autoclave process of Miyata et al. prevents the oxidation of Fe^{+2} to Fe^{+3}, but it does not prevent additional changes in the structure of the suspended compositions to compound (I) undergoing autoclaving to achieve a new composition that is more stable to oxidation. The presence of oxygen in the process of Miyata et al. would produce a Fe^{+3} -containing product that would be different from the product produced under nitrogen.

Miyata et al. also discloses (at Col. 3, lines 33-38) that the hydrothermal treatment under nitrogen causes crystal growth: "The present inventors presume that the hydrothermal treatment at about 100° to about 200° C in the aqueous medium brings about a greater growth of the crystals of the compound of formula (I), a reduction in its surface area and a reduction in lattice

defects." In contrast, in the current invention, crystal growth is not desired. The product of Miyata et al. is millimeter sized (see Col. 9, lines 50-51: "...each of the spherical dried products having a diameter of 2 mm obtained under the different hydrothermally treating conditions..."), whereas the composition undergoing autoclaving in the current invention consists of a suspension of particles of submicron to micron size.

Both change in the composition as a result of autoclaving under nitrogen and the increase of crystal growth as a result of autoclaving under nitrogen can be acceptable for the oral dosage forms disclosed in iron II compounds of Miyata et al. These compounds are used for oral administration [see Col. 1, line 50; Col. 7, line 49; Col. 7, line 68; Col. 8, lines 4-5; Col. 11, line 36; Col. 12, line 4; and Claim 9; e.g., "The iron deficiency treating agent of the invention may be in various forms, such as powders, granules, pills, tablets, capsules, suspensions and emulsions. It may also be in the form of pastes, chewing gums and drinks." (see Col. 8, lines 15-19)]. However, the phenomena of change in composition and of increased crystal growth are contrary to the objectives for injectable use of the current invention, wherein no change in the compound being autoclaved is desired for injectable use, and wherein substantial growth in crystal size is to be avoided for injectable use.

Thus, although nitrogen is used to prevent oxidation of iron II and iron III, Miyata et al. teaches away from the critical components of the current invention and would lead one skilled in the art to expect both a change in chemical composition of the compound subjected to autoclaving under nitrogen plus an increase in crystal particle size of the suspension subjected to autoclaving under nitrogen.

The Office Action has failed to make a prima facie case for obviousness. The combination of Miyata et al. and Muller et al. does not suggest to those skilled in the art the presently claimed invention.

In view of the foregoing, the obviousness rejection of claims 21 to 46, 48 to 54 and 56-57 should be withdrawn.

Applicants have amended claims 38 and 39 to recite phosholipid surface modifier.

Claims 21, 22, 38, and 39 have been amended to recite the amount of thermoprotectant and the amount of drug particles. Further, claims 38 and 39 have been amended to recite the amount of the surface modifier and the particles size of the drug particles. In view of the foregoing, the section 112, first paragraph, rejections of claims 38-54 and 56-57 and claims 21-22 should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: 3/21/03

PATENT
Attorney Docket No. 401730/SKYEPHARMA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

AWADHESH K. MISHRA

Application No. 09/321,766 Art Unit: 1617

Filed: May 28, 1999 Examiner: E. J. Webman

For: THERMOPROTECTED COMPOSITIONS AND PROCESS FOR TERMINAL STEAM STERILIZATION OF MICROPARTICLE PREPARATIONS

AMENDMENTS TO CLAIMS MADE IN RESPONSE TO OFFICE ACTION DATED SEPTEMBER 23, 2002

21. (Twice Amended) An autoclavable composition of an aqueous injectable terminally steam sterilized suspension in a vial sealed under nitrogen atmosphere, said suspension containing particles of a water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3 μm with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25 μm or greater size, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol and mixtures thereof, the ratio of said active substance to said phospholipid surface modifier is from about ~~1:1 to 5:1~~ 3:1 to about 5:1 and the amount of said phospholipid surface modifier is in the range from about 0.2% w/w to about 5.0% w/w, wherein said composition is ~~substantially completely~~ devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier, said composition is ~~substantially~~ devoid of surfactant additives which coagulate on steam sterilization, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and the ratio of the amount of the active substance and the thermoprotecting agent selected to provide particle size stability during and after terminal steam sterlization.

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22. (Twice Amended) An autoclavable composition of an injectable non-flocculating aqueous terminally steam sterilized suspension under nitrogen in a sealed vial, said suspension containing particles of a water insoluble or poorly soluble drug substance with a volume weighted mean particle size of up to 3 μm with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25 μm or greater size, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, the ratio of said drug substance to said surface modifier is ~~1:1 to 5:1~~about 3:1 to about 5:1, the amount of said surface modifier is in the range from about 0.2% w/w to about 5.0% w/w, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and wherein said composition is ~~substantially completely~~ devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier and ~~substantially~~ devoid of surfactant additives which coagulate on steam sterilization, and the ratio of the amount of the active substance and the thermoprotecting agent selected to provide particle size stability during and after terminal steam sterlization.

26. (Amended) The composition of ~~claims~~claim 21 or claim 22, wherein the phospholipid surface modifier is selected from the group consisting of natural phospholipids and synthetic phospholipids.

30. (Amended) The composition of claim 29, wherein the antifungal agent is ~~intraconazole~~itraconazole.

35. (Amended) ~~A~~The composition according to claim 22, wherein the water-insoluble or poorly water-soluble drug substance is suitable for either immediate release or sustained release delivery of said drug substance by parenteral administration.

38. (Amended) An aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, from about 0.2% w/w to about 5% w/w of one or more phospholipid surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, sealed in a vial under nitrogen atmosphere, said suspension containing particles of the water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3μm, with not more than 3000 particles of 10μm or greater

size and not more than 300 particles of 25μm or greater size, wherein the ratio of the amount of the active substance to the phospholipid surface modifier and/or the thermoprotecting agent being selected so as to provide particle size stability during and after terminal steam sterilization, and the particle size subsequent to terminal steam sterilization is not more than about two-fold of the volume weighted mean particle size prior to the terminal steam sterilization, and the suspension is devoid of surfactants which coagulate on steam sterilization.

39. (Amended) An aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, from about 0.2% w/w to about 5% w/w of one or more phospholipid surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, sealed in a vial under nitrogen atmosphere, said suspension containing particles of the water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3μm, with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25μm or greater size, the ratio of the amount of the active substance to the phospholipid surface modifier and/or the thermoprotecting agent being selected to provide particle size stability during and after terminal steam sterilization wherein the particle size subsequent to terminal steam sterilization is not more than about two-fold of the volume weighted mean particle size prior to the terminal steam sterilization, wherein the suspension is substantially devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud point modifier for further stabilization and the suspension is devoid of surfactants which coagulate on steam sterilization.

44. (Amended) The suspension of claim 38, wherein the one or more phospholipid surface modifiers are natural phospholipids or synthetic phospholipids.

46. (Amended) The suspension of claim 38, wherein the amount of the surface modifier provides a biologically active substance to surface modifier ratio of ~~up~~3:1 to 5:1.

48. (Amended) The suspension of claim 38, wherein the composition also contains a pharmaceutical excipient ~~suitable~~ for opthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble bioligical active substance.

56. (Amended) The suspension of claim 38, wherein the water-insoluble or poorly water-soluble biologically active substance is at a pharmaceutically acceptable concentration ~~suitable~~

for either immediate release or sustained release delivery of the active substance by parenteral administration.

PATENT
Attorney Docket No. 401730/SKYEPHARMA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

AWADHESH K. MISHRA

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For: THERMOPROTECTED COMPOSITIONS AND PROCESS FOR TERMINAL STEAM STERILIZATION OF MICROPARTICLE PREPARATIONS

PENDING CLAIMS AFTER AMENDMENTS MADE IN RESPONSE TO OFFICE ACTION DATED SEPTEMBER 23, 2002

21. An autoclavable composition of an aqueous injectable terminally steam sterilized suspension in a vial sealed under nitrogen atmosphere, said suspension containing particles of a water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3 μm with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25 μm or greater size, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol and mixtures thereof, the ratio of said active substance to said phospholipid surface modifier is from about 3:1 to about 5:1 and the amount of said phospholipid surface modifier is in the range from about 0.2% w/w to about 5.0% w/w, wherein said composition is devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier, said composition is devoid of surfactant additives which coagulate on steam sterilization, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and the ratio of the amount of the active substance and the thermoprotecting agent selected to provide particle size stability during and after terminal steam sterlization.

22. An autoclavable composition of an injectable non-flocculating aqueous terminally steam sterilized suspension under nitrogen in a sealed vial, said suspension containing particles of a water insoluble or poorly soluble drug substance with a volume weighted mean particle size of up to 3 μm with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25 μm or greater size, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, the ratio of said drug substance to said surface modifier is about 3:1 to about 5:1, the amount of said surface modifier is in the range from about 0.2% w/w to about 5.0% w/w, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and wherein said composition is devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier and devoid of surfactant additives which coagulate on steam sterilization, and the ratio of the amount of the active substance and the thermoprotecting agent selected to provide particle size stability during and after terminal steam sterlization.

23. The composition of claim 21 or claim 22, wherein the suspension also includes a non-surfactant additive to adjust osmotic pressure.

24. The composition of claim 21 or claim 22, wherein the suspension can be diluted with water for parenteral administration.

25. The composition of claim 22, wherein the polyhydroxy compound is selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol, and mixtures thereof.

26. The composition of claim 21 or claim 22, wherein the phospholipid surface modifier is selected from the group consisting of natural phospholipids and synthetic phospholipids.

27. The composition of claim 26 wherein the natural phospholipid is an egg phospholipid or soy phospholipid.

28. The composition of claim 22, wherein the suspension also contains a pharmaceutical excipient for ophthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble drug substance.

29. The composition of claim 21, wherein the active substance is an antifungal agent.

30. The composition of claim 29, wherein the antifungal agent is itraconazole.

31. The composition of claim 21, wherein the active substance is an immunosuppressive agent.

32. The composition of claim 21, wherein the active substance is a sterol.

33. The composition of claim 32, wherein the sterol is alfaxalone.

34. A lyophilized or spray dried powder prepared from the composition of claim 22.

35. The composition according to claim 22, wherein the water-insoluble or poorly water-soluble drug substance is suitable for either immediate release or sustained release delivery of said drug substance by parenteral administration.

36. The composition of claim 35, wherein the parenteral administration is intramuscular, intravenous, or subcutaneous administration.

37. The composition of claim 31, wherein the immunosuppressive agent is a cyclosporin.

38. An aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, from about 0.2% w/w to about 5% w/w of one or more phospholipid surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, sealed in a vial under nitrogen atmosphere, said suspension containing particles of the water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3μm, with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25μm or greater size, wherein the ratio of the amount of the active substance to the phospholipid surface modifier and/or the thermoprotecting agent being selected so as to provide particle size stability during and after terminal steam sterilization, and the particle size subsequent to terminal steam sterilization is not more than about two-fold of

the volume weighted mean particle size prior to the terminal steam sterilization, and the suspension is devoid of surfactants which coagulate on steam sterilization.

39. (Amended) An aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, from about 0.2% w/w to about 5% w/w of one or more phospholipid surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, sealed in a vial under nitrogen atmosphere, said suspension containing particles of the water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3μm, with not more than 3000 particles of 10μm or greater size and not more than 300 particles of 25μm or greater size, the ratio of the amount of the active substance to the phospholipid surface modifier and/or the thermoprotecting agent being selected to provide particle size stability during and after terminal steam sterilization wherein the particle size subsequent to terminal steam sterilization is not more than about two-fold of the volume weighted mean particle size prior to the terminal steam sterilization, wherein the suspension is substantially devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud point modifier for further stabilization and the suspension is devoid of surfactants which coagulate on steam sterilization.

40. The suspension of claim 38, wherein the pH of the suspension before terminal steam sterilization is from about 5 to about 9.

41. The suspension of claim 38, which also includes a non-surfactant additive to adjust osmotic pressure of the suspension.

42. The suspension of claim 38, which also includes an amount of a non-surfactant additive such that, on diluting the suspension with a pharmaceutically acceptable diluent suitable for parenteral administration to a pharmaceutically acceptable concentration for parenteral administration, a suitable osmotic pressure of the diluted suspension results.

43. The suspension of claim 38, wherein the thermoprotecting agent is selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol, and mixtures thereof.

44. The suspension of claim 38, wherein the one or more phospholipid surface modifiers are natural phospholipids or synthetic phospholipids.

45. The suspension of claim 44, wherein the natural phospholipid is an egg phospholipid or soy phospholipid.

46. The suspension of claim 38, wherein the amount of the surface modifier provides a biologically active substance to surface modifier ratio of 3:1 to 5:1.

48. The suspension of claim 38, wherein the composition also contains a pharmaceutical excipient for opthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble bioligical active substance.

49. The suspension of claim 38, wherein the active substance is an antifungal agent.

50. The suspension of claim 49, wherein the antifungal agent is itraconazole.

51. The suspension of claim 38, wherein the active substance is an immuno-suppressive drug.

52. The suspension of claim 51, wherein the immuno-suppressive drug is a cyclosporin.

53. The suspension of claim 38, wherein the active substance is a sterol.

54. The suspension of claim 53, wherein the sterol is alfaxalone.

56. The suspension of claim 38, wherein the water-insoluble or poorly water-soluble biologically active substance is at a pharmaceutically acceptable concentration for either immediate release or sustained release delivery of the active substance by parenteral administration.

57. The suspension of claim 56, wherein the parenteral administration is intramuscular, intravenous, or subcutaneous administration.